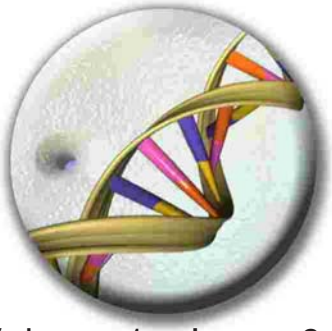

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Transcriptions

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Indiana State Department of Health

Inside this issue

Fetal Alcohol Spectrum Disorders (FASDs)

The umbrella phrase "fetal alcohol spectrum disorders" (FASDs) describes the range of effects that can occur in a person whose mother drank alcohol while pregnant. The term FASD is not intended for use as a clinical diagnosis, but rather refers to any one of the spectrum disorders. (CDC)

Fetal alcohol syndrome (FAS) is the leading known preventable cause of mental retardation and birth defects. If a woman drinks alcohol during her pregnancy, her baby can be born with FAS, a lifelong condition that causes physical and mental disabilities and problems with behavior or learning. Often, a person has a mix of these problems.

Approximately one out of every 100 children has a FASD. Of the disorders within the range of FASDs, the most severe is FAS, which affects approximately one out of every 1,000 children. The National Organization on Fetal Alcohol Syndrome (NOFAS) has stated: "Fetal Alcohol Syndrome (FAS), the most severe and least common effect under the FASD umbrella, costs the United States $5.4 billion annually in direct and indirect costs.....potential savings from preventing one case of FAS would result in a $300,000 reduction in medical costs alone."

The mission of the Indiana FASD Prevention Task Force is to achieve 100 percent prevention of these disorders. With even moderate prevention outcomes, the impact on the health of Indiana children would be remarkable. The financial and emotional burden on a variety of systems, including the criminal justice and medical care systems, as well as schools and social service agencies, would be substantially alleviated.

The Indiana FASD Prevention Task Force is working to develop real-world strategies aimed at increasing awareness, prevention efforts, and education. This article will address FASD definitions, diagnostic issues, and recommendations regarding treatment, prevention, and education.

Etiology

Prenatal exposure to alcohol is a factor common to each fetal alcohol disorder. A health article by Anne George described that:

> "It is now known that alcohol is a teratogen, that is, it causes malformations in the developing embryo. Scientific knowledge changed when French (Leone et at., 1968) and American researchers (Jones and Smith, 1973; Cleland, 1972) reported on patterns of malformation in infants born to mothers who drank excessively."

(Gale Encyclopedia of Public Health, 2002, www.healthline.com, retrieved 8/30/2007)

continued on page 2

Special Challenges, Special Opportunities: Children with a FASD and School

The school experience can be frustrating for the child who suffers from a fetal alcohol spectrum disorder (FASD) and can also be frustrating for teachers. However, an understanding of symptoms and attainment of knowledge and skills regarding implementation of effective teaching strategies can be very beneficial. It can serve to maximize rewards for the student and increase teacher satisfaction as a result of their enhanced skill arsenal.

Continued on page 3

2 Fetal Alcohol Spectrum Disorders (FASDs) *continued from page 1*

Although every child with a FASD was prenatally exposed to alcohol, not every infant exposed to alcohol prenatally will have a FASD. It has not been definitively established how much alcohol a woman needs to consume to have an affected baby. The *FAS: Guidelines for Referral and Diagnosis* chronicled that: "The learning and life skills affected by prenatal exposure vary greatly among individuals, depending on the amount of alcohol exposure and the timing and pattern of exposure, as well as each individual's current and past environment." (p. 22) Refraining from ingesting alcohol prior to conception and throughout the pregnancy is the only certain way to prevent FASDs.

Diagnostics

In 2002, Congress directed the Centers for Disease Control (CDC) to (1) develop guidelines for diagnosing FAS and other negative birth outcomes resulting from prenatal exposure to alcohol, (2) incorporate these guidelines into curricula for medical and allied health students and practitioners, and (3) disseminate curricula concerning these guidelines to facilitate training of medical and allied health students and practitioners. (*Guidelines for Identifying and Referring Persons with Fetal Alcohol Syndrome*, *MMWR*, October 2005) Diagnostic guidelines were developed based on recommendations by the scientific working group convened by the CDC.

According to the CDC, a diagnosis of FAS should be made if documentation exists for the presence of (1) all three dysmorphic facial features (i.e. smooth philtrum, thin vermillion border, and small palpebral fissures), (2) prenatal or postnatal growth deficit in height or weight, (3) at least one CNS abnormality, which may be documented as structural, neurological, or functional, and (4) confirmed prenatal alcohol exposure or unknown prenatal alcohol exposure. *(FAS: Guidelines for Referral and Diagnosis, National Center on Birth Defects and Developmental Disabilities, et al, 3rd printing, May 2005. p. 19; MMWR, October, 2005)* **Note:** The CDC's *FAS: Guidelines for Referral and Diagnosis* states that "guidelines could be expanded or refined to include other alcohol-related disorders", such as alcohol-related neurodevelopmental disorder (ARND), and alcohol related birth defects (ARBD) (p. 4). Currently, efforts are being made to establish standardized national diagnostic criteria. Although there is no consensus regarding diagnostic criteria for disorders on the spectrum, there are many similarities and intersects amongst the models that have been developed.

Comparison of Models

The following table highlights a basic summary of three of the most commonly used models of FAS diagnostic criteria. A comparison of these models provides a more definitive universal clinical picture.

Key Diagnostic Areas	Institute of Medicine (1996)	4-Digit Code* (2004)	Centers for Disease Control (2004)
Growth	**One or more of the following:** • Low wt. for ht. • Low birth weight • Decelerating wt.	• Pre or postnatal ht. or wt. ≤ 3rd percentile (%ile)	• Pre or postnatal ht. or wt. ≤ 10th (%ile)
Face	**Characteristic pattern of features including:** • Short PFL • Flat upper lip • Flattened philtrum • Flat mid-face	**All three required** • PFL ≤ 3rd %ile • Philtrum • Lip	**All three required** • PFL ≤ 10th %ile • Philtrum (Rank 4-5) • Lip (Rank 4-5)
CNS	**One or more of the following:** **Structural:** OFC ≤ 3rd %ile, abnormal structure **Neurological:** Hard/soft signs	**One or more of the following:** **Structural:** OFC ≤ 3rd %ile, abnormal structure **Neurological:** Hard signs, seizure disorder **Functional:** 3+ domains with impairment ≥ 2 SDs below mean **Global Deficits**	**One or more of the following:** **Structural:** OFC ≤ 10th %ile, abnormal structure **Neurological:** Hard signs, seizure disorder **Functional:** 3+ domains with impairment ≥ 1 SDs below mean **Global Deficits**
Alcohol Exposure	**Confirmed/unknown**	**Confirmed/unknown**	**Confirmed/unknown**

Adapted from table by Susan Astley, PhD, University of Washington, Seattle, NSCG Education Conference Prg. Bk., 2006, p. 53
Abbreviations: wt = weight; ht = height; PFL = palpebral fissure length; CNS = central nervous system; OFC = occipitofrontal circumference
*Developed from sample of 1014 children diagnosed with FASD through the Washington State FASD Diagnostic and Prevention Network at the University of Washington in Seattle. The four digits in the code reflect the magnitude of expression of the four key diagnostic features of FAS in the following order: (1) growth deficiency, (2) FAS facial features, (3) CNS dysfunction, and (4) prenatal alcohol exposure. Each feature is ranked on a Likert scale of 1 (complete absence of feature) to 4 ("classic" presence of feature).

(continued on page 3)

Recommendations of the Indiana FASD Task Force

The Indiana FASD Prevention Task Force is working to facilitate more effective and comprehensive identification, treatment, and prevention of these disorders. In 2006, the Indiana FASD PreventionTask Force conducted a *FASD Needs Assessment* and subsequently developed the *Indiana FASD Strategic Plan*. Objectives identified through this process included increasing public awareness, educating communities about FASD prevention, and supporting communities in the development of prevention campaigns. The following recommendations were designed to be integrated with these objectives:

- Work with partners to establish and raise awareness about definitive diagnostic criteria for FAS for use by Indiana physicians.
- Work with physicians and other diagnosticians to collect data on FASDs for the Indiana Birth Defects and Problems Registry to support individual families and for epidemiological research.
- Develop and implement prevention education curricula in middle and high school classes.
- Develop training strategies to increase awareness for professionals outside the healthcare field (e.g. school staff and faculty).
- Work to develop and implement statewide prevention marketing strategies.
- Evaluate screening, prevention, and professional education programs on an ongoing basis for process improvement.

Conclusion

Beyond the fact that FASDs are 100% preventable, much can be done to improve diagnosis and treatment. Earlier recognition of FASDs would allow for implementation of strategies that could serve to maximize abilities of the child, mitigate the effects of the condition, and reduce the child's frustrations in home and school environments. Education about FASDs and implementation of strategies in collaborative environments could also benefit caretakers and professionals by increasing their sense of efficiency. Barriers related to transition to adulthood could also be mitigated through continued collaboration.

Resources

Centers for Disease Control and Prevention: *www.cdc.gov/ncbddd/fas*
FAS Community Resource Center (FASCRC): *www.come-over.to/FASCRC*
Fetal Alcohol Syndrome Family Resource Institute (FASFRI): *fetalalcoholsyndrome.org*
Journal of FAS International: *www.motherisk.org/JFAS*
National Organization of Fetal Alcohol Syndrome (NOFAS): *www.nofas.org*
SAMHSA's FASD Center for Excellence: *fascenter.samhsa.gov*

Special Challenges, Special Opportunities: Children with a FASD and School continued from page 1

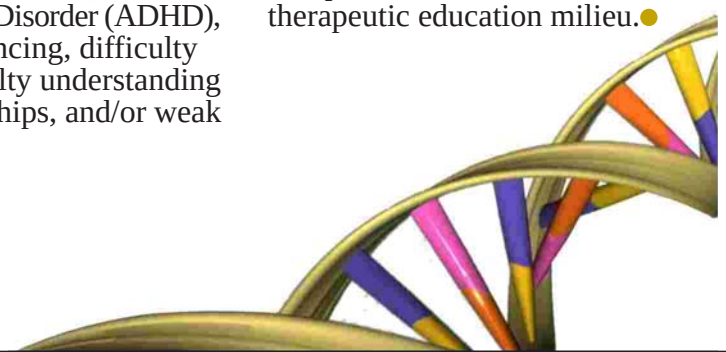
The government of British Columbia, Ministry of Education, developed a primer with useful information about teaching students with fetal alcohol syndrome (FAS). Although there has been an increasing awareness of the effects of alcohol use during pregnancy on unborn children for centuries, the Ministry of Education states:

> "It was not until 1973, however, that the scientific community recognized the distinctive pattern of delayed growth, intellectual and behavioral disabilities, and facial characteristics caused by alcohol abuse during pregnancy and gave it the name Fetal Alcohol Syndrome (FAS). Since that time, public awareness of this neurological disorder has been growing. A diagnosis of FAS is made when there is known significant prenatal exposure to alcohol and the child exhibits three characteristics: delayed prenatal or postnatal growth, central nervous system involvement, and characteristic facial features." (www.bced.gov.bc.ca)

It is important to remember that FASD connotes varying degrees and types of symptoms. Although one out of 1,000 children may suffer from the more severe FAS, it has been estimated that one out of 100 children may suffer, to some degree, from the broader spectrum of fetal alcohol disorders. The BC Ministry of Education states that students with FAS can have an IQ ranging from 29—120; students with Fetal Alcohol Effects (FAE) can have IQs ranging from 42—142. The Ministry describes that children with a FASD may have other conditions, which may include learning disabilities, Attention Deficit/Hyperactivity Disorder (ADHD), difficulty with sequencing, difficulty with memory, difficulty understanding cause/effect relationships, and/or weak generalizing skills.

There are a number of other areas where students with a FASD may experience difficulties, including social/emotional and physical functioning. Teachers who have an awareness of these problems may be better able to develop effective program plans, thereby setting these children up for success by drawing on their strengths and maximizing development of their talents.

Additionally, teachers with insight into fetal alcohol disorders will be able to develop strategies and an understanding that ongoing behavioral and cognitive presentation of their students who have a spectrum disorder would be expected and accepted in the context of the therapeutic education milieu.



4 Metabolic and Genetic Factors Contributing to Alcohol-Related Effects and Fetal Alcohol Syndrome

At a glance

Within this article, Gemma *et al* propose that maternal genotype may alter the risk of fetal alcohol spectrum disorders (FASD) by changing the rate of ethanol metabolism. The authors evaluated these differing metabolic rates by measuring the activity of certain polymorphic forms of two enzymes (ADH and CYP2E1) involved in alcohol metabolism. The authors also discuss the effect the placental activity of these enzymes have on fetal susceptibility to prenatal alcohol exposure.

Introduction

Because of FASD's high prevalance within the general population and the increased risk for birth defects and/or neurodevelopmental abnormalities associated with maternal alcohol use, Gemma *et al* state, "...understanding [the] factors responsible for increasing the risk [of FAS] in pregnant women...is a key issue." Currently, the exact causative mechanisms of FASD are not known, due to the intricate interactions between the following factors:

1. the complex effects of alcohol on the body's cells;
2. genetic and molecular signals;
3. the quantity, frequency, and timing of prenatal alcohol consumption;
4. the developmental stage of the fetus;
5. general maternal health;
6. use of other drugs; and
7. other factors as yet unidentified.

Gemma *et al* propose that maternal metabolic activity alters fetal blood alcohol exposure, and that differing maternal metabolic rates may partially explain the range of features seen in children with FASD. Within this article, the authors explore the hypothesis that the differences in metabolic rates are influenced by genetic polymorphisms that alter how certain enzymes participate in alcohol metabolism and xenobiotics.

Enzymes involved in alcohol metabolism

Upon ingestion, alcohol is absorbed by the gastrointestinal tract and metabolized in the liver to ultimately form CO2 and water for elimination from the body. The first step of this process (the conversion of ethanol to acetaldehyde) is catalyzed mainly by alcohol dehydrogenase (ADH). Approximately 10% of alcohol is normally metabolized by another enzyme, CYP2E1; if ADH becomes saturated (due to larger doses of alcohol or long-term alcohol use), CYP2E1 activity increases.

Numerous genes coding for ADH and CYP2E1 have been identified; at least one study has reported that polymorphisms within these genes alter enzyme activity, and, therefore, the metabolism of alcohol and its toxic metabolites.[1] In addition, the different frequencies of these genes in various ethnic populations may provide protective or enhancing factors for alcohol-related birth defects.

Alcohol dehydrogenase (ADH) & CYP2E1

Approximately 3% of all functional ADH is located in the liver.[2] Seven genes on chromosome 4 code for ADH, resulting in five possible classes (I–V) of molecular forms with unique physical and chemical properties. Class I ADH comprises the majority of hepatic ADH, and is the focus of Gemma *et al*'s discussion. Currently, no relevant polymorphisms for classes II – V have been reported.[3]

Although multiple isoenzymes of class I ADH exist, polymorphisms within *ADH2* (encoding the β subunits) are the only changes reported to significantly alter the enzyme's activity.[2] *ADH2* can be further divided into *ADH2*1*, *ADH2*2*, and *ADH2*3* (the β1, β2, and β3 subunits, respectively) due to single nucleotide changes that create subunits with vastly different physical and catalytic properties. Persons expressing β1 or β3 subunits are thought to have faster and more efficient alcohol clearance rates than individuals expressing neither.[3] A study performed in the Western Cape Province of South Africa (a population with a prevalence of 39 – 46 FAS cases per 1,000 births) reported that persons without FAS are more likely to have the *ADH2*2* (β2) allele, suggesting that this subunit provides some protection against the development of FAS.[4] Gemma *et al* state that their hypothesis is corroborated by the latter study, which demonstrates that persons with ADH variants that increase enzyme activity have lower rates of overall maternal alcohol consumption.

The *ADH2*3* (β3) isoform, unique to the African-American population, has been shown to provide protection against prenatal alcohol exposure via more efficient ethanol metabolism.[5] Another study found that *ADH2*3* (β3) was protective against abnormal facies in offspring prenatally exposed to alcohol.[6] Based upon these and other studies, Gemma *et al* state, "...the presence of either *ADH2*2* and *ADH2*3* variants appears to influence alcohol-derived teratogenesis," but acknowledge that currently, the explanation for this association is not known.

The authors suggest that other genetic and/or environmental factors, such as the effect of alcohol on retinoic acid synthesis, are likely to play a role in the development of FASD. Retinoic acid is synthesized from vitamin A in a reaction catalyzed by ADH classes I and IV. Substrate competition between ethanol and vitamin A during embryonic development may result in a transient decrease in the level of vitamin A. This, in turn, would prevent formation of normal neural crest cells and ultimately alter all structures derived from neural crest cells. In support of this proposition, Gemma *et al* report that children with vitamin A deficiency have a phenotype strikingly similar to the FASD phenotype.

A single gene on chromosome 10

continued on page 5

continued from page 4

codes for CYP2E1, which catalyzes the oxidation of alcohol and produces reactive oxygen species, which lead to oxidative stress, DNA damage, and cell death. Significant levels of activated CYP2E1 have been identified in brain tissue during embryogenesis and organogenesis. Chronic alcohol consumption may result in further activation of CYP2E1, resulting in amplified production of reactive oxygen species and, subsequently, increasing the rate of cell death in the fetal brain.[2]

Ten polymorphic loci on the *CYP2E1* gene have been identified to date.[2] One study reported that a variant CYP2E1 allele was found in 31 percent of the African-American population and 7 percent of Caucasians.[5] Despite the fact that most studies involving CYP2E1 to date have examined its contribution to the development of alcoholism and not FASD, Gemma *et al* report that the high frequency of this gene in the population necessitates further evaluation of its relationship to the development of FASD.

Placental enzymes

In addition to barring certain toxic substances, the placenta contains enzymes which have the ability to metabolize alcohol and other substances that cannot be physically blocked from entering fetal circulation. Gemma *et al* state that placental CYP2E1 plays a larger role in alcohol metabolism than placental ADH, since the latter has a lower affinity for alcohol. Placental CYP2E1 activity has been proposed as one factor contributing to the range of birth defects seen in children prenatally exposed to alcohol. Maternal genotype may regulate the degree to which alcohol induces placental CYP2E1 activity, which subsequently may increase or decrease fetal susceptibility to alcohol-related birth defects; however, Gemma *et al* acknowledge that other regulatory mechanisms are likely to participate in this process.

Conclusion

Understanding some of the metabolic and genetic factors which influence the development of alcohol-related birth defects may be a key step toward prevention of FASD. For all future studies, the authors stress the importance of utilizing standard approaches and uniform methods of categorization in order to generate data of quality.

Overall, Gemma *et al* state, "Although at present no clear-cut conclusions can be drawn, there is an increasing amount of information suggesting that allelic variants encoding for...enzymes involved in ethanol metabolism put some...populations at high risk of having an affected child."●

Written by
Gemma S., Vichi S., & Testai E.
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31: 221—229. 2007.
Summary provided by
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References

1 Agarwal DP. Genetic polymorphisms of alcohol metabolizing enzymes. *Pathologie Biologie* 49: 703-709. 2001.
2 Gemma S, Vichi S, and Testai E. Individual susceptibility and alcohol effects: biochemical and genetic aspects. *Ann 1st Super Sanita* 42(1): 8-16. 2006.
3 Arfsten DP, Silbergeld EK, Loffredo CA. Fetal ADH2*3, maternal alcohol consumption, and fetal growth. *International Journal of Toxicology* 23: 47-54. 2004.
4 Viljoen DL *et al*. Alcoholism. *Clinical and Experimental Research* 25: 1719-1722. 2001.
5 McCarver DG *et al*. Alcohol dehydrogenase-2*3 allele protects again alcohol related birth defects among African Americans. *Journal of Pharmacology and Therapeutics* 283: 1095- 1101. 1997.
6 Das UG *et al*. Alcohol dehydrogenase 2*3 affects alterations in offspring facial morphology associated with maternal ethanol intake in pregnancy. *Alcoholism—Clinical and Experimental Research* 28: 1598-1606. 2004.

Quotes and Numbers of Note

Fetal Alcohol Spectrum Disorders are 100% Preventable!

- "Fetal Alcohol Spectrum Disorders (FASDs) is an umbrella term describing the range of effects that can occur in an individual whose mother drank alcohol during pregnancy. These effects may include physical, mental, behavioral and learning disabilities with possible lifelong implications. The term FASD is not intended for use as a clinical diagnosis." *(The National Taskforce on FAS and FAE, 2004)*
- "Ancient references to [FASDs] can be seen in the Old Testament of the Bible and in the writings of the Greek philosopher Aristotle. In 1735, the College of Physicians in England warned Parliament of the effects of prenatal maternal alcohol consumption on children." *(History of Fetal Alcohol Spectrum Disorders, NOFAS, Univ. of South Dakota, Center for Disabilities)*
- "Schools exercise a powerful influence over young people, making them ideal settings to educate about the dangers of underage drinking and sexual activity...Of all the substances of abuse (including cocaine, heroin and marijuana), alcohol produces by far the most serious neurobehavioral effects in the fetus." *(NOFAS, Handout: "What School Systems Should Know About Prevention")*
- "Sixty-one percent of adolescents and 58% of adults with a FASD have been in legal trouble." *(NOFAS, Handout: "What the Justice System Should Know")*
- "Fetal Alcohol Syndrome (FAS), the most severe and least common effect under the FASD umbrella, costs the United States $5.4 billion annually in direct and indirect costs...An individual with full-blown FAS incurs an average lifetime health cost of $860,000, although costs can be as high as $4.2 million...Potential savings from preventing 1 case of FAS would result in a $300,000 reduction in medical costs alone." *(NOFAS, Handout: "What the Business Community Should Know")*
- "I have seen one family of children with full-blown FAS nearly bankrupt a county in my home state of Minnesota. The in-home care, special education, legal fees, and healthcare costs that the state was obligated to pay ran in the millions of dollars, all for one household." *(The Honorable Susan Carlson, Juvenile Court Justice, Minnesota)* ●

6 Facts from the National Organization on Fetal Alcohol Syndrome

FASDs are the leading known preventable cause of mental retardation and birth defects.

FASDs affect one in 100 live births, or as many as 40,000 infants each year.

FASDs are not genetic disorders. Women who do not drink alcohol during pregnancy will not have babies with a FASD. Women who drink alcohol during pregnancy have a risk of having a baby with a FASD.

Visit us on the web:
www.in.gov/isdh/20101.htm

Announcements!

The Indiana FASD Prevention Task Force continues to work for FASD prevention by:

- Developing presentations for middle school and high school students.
- Disseminating information to professional organizations through conferences.
- Marketing strategies focused on prevention of FASDs and other environmental risk factors that may positively impact perinatal health.

The ISDH has published birth defects data for 2003—2005 in the *Birth Defects Research Part A: Clinical and Molecular Teratology* (published December 2007).

Physicians, audiologists, and other health care providers should submit data on birth defects. **It is particularly important for physicians to report data regarding FASDs and Autism because they are not identified at birth.** Birth defects data should be reported to the Indiana Birth Defects and Problems Registry (IBDPR) at: http://www.in.gov/isdh/20571.htm

Data from the IBDPR is used for epidemiological purposes and to provide support to individual families.

Cystic Fibrosis was included in the Newborn Screening Panel with full statewide implementation in January 2008. This increases the total number of conditions for which infants in Indiana are screened to 45 (not including hearing screening). If you have any questions, please call (888) 815-0006.

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